Lipid Lowering Agents
Aeromedical Concerns

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The Problem of Hyperlipidemia in Military Aviators

Hyperlipidemia is one of the major risk factors for coronary heart disease, a disease which, after a long asymptomatic period, may without warning cause sudden incapacitation due to angina, myocardial infarction or death. Hyperlipidemia is fairly common in military aviators, ranging from 30-68.5% in NATO countries.[1] In a survey among Greek fighter pilots, 10% had cholesterol levels over 300 mg/dl.[2]

Lipoprotein Levels

Cholesterol measurement is best performed in hospital chemical pathology departments after a fasting state (12-14 hour overnight fast) to allow concomitant measurement of triglyceride levels. Provided triglyceride levels are < 400 mg/dl (4.5 mmol /L), LDL is calculated according to the Friedewald formula.[3]

LDL= Total Cholesterol - HDL- TG/5

The current definitions of cholesterol and lipo-protein levels are listed in Table 1.

Risk Factors for Cardiovascular disease

The major risk factors for cardiovascular disease are:

a. age (male >45yr, female >55yr or premature menopause
b. family history of premature CHD (first degree male relative <55, first degree female relative < 65)
c. current cigarette smoking
d. hypertension (BP>140/90 mm Hg, or taking antihypertensive medication)
e. low HDL cholesterol (<35 mg/dl)
f. diabetes mellitus

Dietary and Drug Therapy

Dietary and drug therapy can lower cholesterol and prevent coronary heart disease. In particular, LDL cholesterol is strongly associated with atherogenesis and is the usual target for intervention. The indications for initiating dietary and drug therapy, and the suggested target levels, are listed in Tables 2 and 3.[3] However, it must be emphasized that correction of weight, aerobic exercise, and cessation of smoking should be considered part of the overall strategy.

Dietary measures should be pursued for at least 3-6 months before contemplating lipid lowering drugs. On average, around 5% reduction in LDL cholesterol is achievable with dietary therapy.[9] Drug therapy should be reserved for those military aviators at high risk for CHD, in the second and third priorities, where diet and healthy lifestyle measures have failed to achieve target levels.

Major Classes of Lipid Lowering Drugs

The major classes of lipid lowering drugs are:

a. Bile acid sequestrants (cholestyramine, colestipol)
b. Fibric acid derivatives (gemfibrozil, fenofibrate, etc.)
c. HMG-CoA reductase inhibitors, commonly referred to as "statins" (lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin)
d. Others (nicotinic acid, probucol)

Bile acid sequestrants: The bile acid sequestrants currently available include cholestyramine and colestipol. Cholestyramine is dispensed in packets or scoops containing 4g of the active agent. The usual dosage ranges from 16 to 32g daily, taken with fluids in divided doses. Colestipol is dispensed in 5g packets. The usual dosage ranges from 15 to 30g daily in divided doses. These agents

are not absorbed. The major side effects are constipation and difficulty in ingesting the agents because of their bulk. Oddly enough, constipation tends to be a problem at lower dosages, and to decrease as the dosage is increased. Occasionally, cholestyramine can increase plasma triglyceride levels. Bile acid sequestrants have been used for years as the drug of choice for military aviators, and their long-term safety is well established. Compliance has usually been the major problem, even in clinical trials, as resins are not only inconvenient to take but also produce gastro-intestinal side effects. Because of the difficulty with compliance, resins may not be the optimal agent for use by aircrew.

Fibric acid derivatives: The most commonly used is gemfibrozil, which has been shown to decrease coronary mortality. Gemfibrozil can be used as first-line therapy in persons with concomitant high triglyceride and low HDL levels. Dosage is 600mg twice a day. Fenofibrate, ciprofibrate and bezafibrate are also used. They can reduce LDL by 20-30%, increase HDL by 10-15%, and reduce triglycerides by 40-60%. The most common side effect is gastrointestinal intolerance; myalgia is a rare complication. Gemfibrozil has also been associated with increased lithogenicity.

HMG-CoA Reductase Inhibitors: The statins are the most potent drugs available for reducing plasma concentration of LDL cholesterol. Statins reduce plasma LDL cholesterol by 30-40%, decrease plasma triglyceride by 10-30%, and increase HDL cholesterol by 2 - 15%. Many statins (pravastatin, atorvastatin, fluvastatin, lovastatin, and simvastatin) have been developed for clinical use and are now available in Europe and the United States.

Simvastatin and lovastatin are administered as lactones, and conversion to the active open acid occurs in the liver. In contrast, pravastatin is administered as a sodium salt of the open acid. Simvastatin is fat soluble, while pravastatin is water soluble and does not appear to cross the blood-brain barrier. Pravastatin has been shown to be minimally detectable in the cerebrospinal fluid of healthy volunteers, whereas lovastatin was present at concentrations that could have a pharmacologic effect.[6] The inability of pravastatin to penetrate into cerebrospinal fluid has been attributed to its hydrophilicity and low affinity for the transport mechanism of the blood-brain barrier.[7] The CNS penetration of lipophilic HMG-CoA reductase inhibitors may have clinical implications that are particularly relevant to military aviators.

The lipid lowering effect of statins is achieved by competitive and reversible inhibition of HMG-CoA reductase in hepatocytes, which induces a reduction in intracellular stores of cholesterol. As a consequence of the decline in cholesterol levels, there is up-regulation of LDL receptors on hepatocyte membranes, resulting in enhanced receptor-mediated catabolism and clearance of atherogenic LDL-cholesterol. Thus the liver is the primary site of action of statins. Administration of statins in the evening is associated with a greater lipid-lowering effect than that seen with morning administration.[5] This is almost certainly due to the increased nocturnal biosynthesis of cholesterol that occurs in humans. Clinically, the most important adverse events associated with HMG-CoA reductase inhibitors are myopathy and increases in hepatic transaminase levels. Myopathy, defined as muscular aching and weakness accompanied by a >10-fold elevation in CPK, is uncommon, occurring in <0.1% of patients in clinical trials of pravastatin.[8] If not recognized, however, myopathy can proceed to rhabdomyolysis and acute renal failure. It is generally recommended that HMG-CoA reductase inhibitor therapy be discontinued in patients developing markedly elevated CPK levels, or in those with symptoms suspicious for myopathy.

In common with other HMG-CoA reductase inhibitors, as well as other lipid-lowering drugs, biochemical abnormalities of liver function may occur with pravastatin therapy. Such increases in serum liver enzyme levels associated with pravastatin therapy routinely resolve on drug discontinuation, and are usually asymptomatic. In the WOSCOPS study, elevated SGOT and SGPT levels (> 3 times upper limit of normal) were present in 0.78% and 0.48% of 3302 pravastatin and 3293 placebo-treated patients, respectively.[8]

Clinical Experience in Primary Prevention of CAD with Lipid Lowering Agents

Five randomized, placebo-controlled trials have examined pharmacologic lipid-lowering therapy for primary prevention. The three early trials (World Health Organization study with clofibrate, LRC-CPPT with cholestyramine, and Helsinki Heart Study with gemfibrozil) showed a significant reduction in the risk of developing coronary events.[10,11]

The two latest trials, WOSCOPS, using pravastatin, and AFCAPS/TexCAPS, using lovastatin, clearly demonstrated reduction (31% and 37%, respectively) in the risk of cardiac death and nonfatal myocardial infarction with statin therapy for primary prevention.[8,12] These data show that lipid-lowering therapy, particularly with statins, can be effective in preventing cardiac events in patients without a previous diagnosis of coronary heart disease. To answer the question of cost-effectiveness for primary prevention we must compare the number of patients needed to treat in order to prevent one CHD death or nonfatal MI. Among patients enrolled in the primary prevention trial AFCAPS/TexCAPS, 83 patients required treatment to prevent one cardiac event. In the primary prevention trial WOSCOPS, treatment of 40 patients prevented one cardiac event. As the risk profile becomes more ominous, the cost-effectiveness increases.

Cholesterol Lowering Therapy and the Central Nervous System

Cholesterol is an important constituent of the central nervous system, which contains about 20% of the non-exchangeable pool of cholesterol in the body. Thus it is pertinent to consider whether lipid lowering therapy that decreases cholesterol synthesis might also adversely affect CNS functions, including emotional, intellectual and organic functions. This aspect of lipid lowering therapy is particularly relevant to military aviators.

Simvastatin and lovastatin, being lipophilic agents, have been shown to cross the blood brain barrier, in contrast to the hydrophilic agent pravastatin. This CNS penetration of HMG-CoA reductase inhibitors may also have clinical implications. Lovastatin and simvastatin, but not pravastatin, have been reported to be associated with sleep disturbance. Also, a recent study[13] suggested that lovastatin significantly affected daytime performance, with divided attention and vigilance worsening, effects that were not observed in the pravastatin group. Neither pravastatin nor lovastatin significantly affected nocturnal sleep or daytime sleepiness. Similar results were reported in later studies.[14,15] However, in a subsequent comparative study of lovastatin and pravastatin there was no significant effect by either drug on sleep or CNS function, including visual reaction time, auditory reaction time, verbal learning, embedded figures tests, verbal fluency test, trail making test, or visual memory test.[16] There are unpublished data about atorvastatin and pravastatin, in which both showed an increase in wakefulness during the latter part of the night, but neither drug appeared to affect subjective sleep assessment or performance.[17]

Conclusion

The basis for the usual therapy of hyperlipidemias, apart from severe and hereditary types, is strict dietary modification. Careful attention to all other coronary risk factors is essential. It is clear from epidemiologic studies that, even in the "normal" range of cholesterol, lower values are associated with fewer cardiovascular events, emphasizing the virtues of dietary advice for aircrew. Drug therapy can be used when dietary management fails or is inappropriate. No ideal lipid-lowering drug has yet been found. Statins are the most effective lipid-lowering agents, and seem to be safe according to large trials. Among the statins, the hydrophilic pravastatin has been preferred for use in aircrew, since both in theory and in studies it does not appear to affect the central nervous system. Whether the minor disturbances in sleep observed with some of the statins is of significance to aircrew involved in intensive operations is unclear at this time.

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TABLE 1: Lipoprotein Levels

Total Cholesterol	
Desirable	<200mg/dl (5.2mmol/L)
Borderline	200-250 mg/dl (5.2-6.5mmol/L)
High	>250mg/dl (6.5mmol/L)
LDL Cholesterol	
Desirable	<130mg/dl (3.4mmol/L)
Borderline	130-160mg/dl (3.5-4.1mmol/L)
High risk	>160mg/dl (5mmol/L)
HDL Cholesterol	
Low	<35mg/dl (0.9mmol/L)

TABLE 2: Indications for Initiating Dietary Therapy, and the Suggested Target Levels

		Total Cholesterol (mg/dl)		LDL Cholesterol (mg/dl)	
Priority	**Subject Category**	**Initiation Level**	**Target Level**	**Initiation Level**	**Target Level**
First	CHD	>200	<200	>100	<100
Second	**Without CHD, and with 2 or more risk** factors, or genetically determined hyperlipidemia	**>250**	**<200**	**>130**	**<130**
Third	Without CHD and with fewer than 2 risk factors	>300	<200	>160	<160

TABLE 3: Indications for Initiating Drug Therapy, and the Suggested Target Levels (mg/dl)

		Total Cholesterol (mg/dl)		LDL Cholesterol	
Priority	**Subject Category**	**Initiation Level**	**Target Level**	**Initiation Level**	**Target Level**
First	CHD	>200	<200	>130	<100
Second	Without CHD, and with 2 or more risk factors, or genetically determined hyperlipidemia	>250	<200	>160	<130
Third	Without CHD and with fewer than 2 risk factors	>300	<200	>190	<160

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